UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	19

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/977,787	Applicant(s) MIZZEN ET AL.	
	Examiner Mary K Zeman	Art Unit 1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☒ Responsive to communication(s) filed on *14 April 2000 and 24 May 2000* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *54-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *54-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15)☐ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18)☐ Interview Summary (PTO-413) Paper No(s). _____
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other:

DETAILED ACTION

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1631.

Claims 54-67 are pending in this application. Claims 1-5, 13-41 and 43-49 have been canceled.

Applicant's arguments filed 4/14/2000 have been fully considered but they are not completely persuasive. All non-reiterated rejections have been withdrawn.

Claim Objections

Claim 66 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. Claim 66 depends from claim 64, and from claims 55-62. It is suggested that the claim be amended to recite all of the relevant limitations of claim 64 as an independent claim. See MPEP § 608.01(n).

Claims 57, 58, and 60 are objected to because of the following informalities: the claims recite a variety of abbreviations which should be spelled out at their first instance in the claims, in the interests of clarity. For example, "pg75" in claim 60 would appear to be a typographical error for "gp75", but that cannot necessarily be assumed. Also, would any protein of 100kd fulfill the antigen "p100"? Further in Claim 58, the recitations "pET65MP/NP-B" and "pET65M/NP/D" appear to be names of plasmids which encode fusion proteins, and are not the designations of the proteins themselves. Appropriate correction is required.

Rejections Maintained

The declaration filed on 5/24/2000 under 37 CFR 1.131 has been considered but is ineffective to overcome the Suzue reference. The declaration does not state that the work was done in the USA, a WTO country or a NAFTA country as defined in and required by MPEP 715. A declaration satisfying the conditions of 37 CFR 1.131(a), and having the same evidence and arguments present in the instant declaration would be sufficient to overcome the reference.

> MPEP 715 states: "37 CFR 1.131(a) has been amended to implement the relevant provisions of Public Law 103-182, 107 Stat. 2057 (1993) (North American Free Trade Agreement Act) and Public Law 103-465, 108 Stat. 4809 (1994) (Uruguay Round Agreements Act), respectively. Under 37 CFR 1.131(a) as amended, which provides for the establishment of a date of completion of the invention in a NAFTA or WTO member country, as well as in the United States, an applicant can establish a date of completion in a NAFTA member country on or after December 8, 1993, the effective date of section 331 of Public Law 103-182, the North American Free Trade Agreement Act, and can establish a date of completion in a WTO member country other than a NAFTA member country on or after January 1, 1996, the effective date of section 531 of Public Law 103-465, the Uruguay Round Agreements Act (URAA). Acts occurring prior to the effective dates of NAFTA or URAA may be relied upon to show completion of the invention; however, a date of completion of the invention may not be established under 37 CFR 1.131 before December 8, 1993 in a NAFTA country or before January 1, 1996 in a WTO country other than a NAFTA country."

Claims 54, 55, 59, 61-67 remain rejected under 35 U.S.C. 102(a) as being anticipated by Suzue (PTO-1449 reference AR).

Suzue (Journal of Immunology 1996 vol 156 pages 873-879) discloses a fusion protein comprising HIV p24 in fusion with hsp70. This composition elicited both humoral and cellular (cytolytic) responses when administered to mice in an adjuvant-free saline solution (see abstract, Figure 1B). Saline is a pharmaceutically acceptable carrier or diluent. The fusion of the two

proteins (hsp and p24) was determined to be necessary for proper immune stimulation (See paragraph bridging pages 876-877). Accordingly, Suzue anticipates the claimed invention.

Claims 56-58 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Roman et al (Immunology 88(4): 487-492, August 1996), in view of Suzue (Journal of Immunology 1996 vol 156 pages 873-879 PTO-1449 reference AR).

The claims state that the antigen is an influenza antigen in fusion with the stress protein.

Roman et al. teaches that synthetic peptides non-covalently bound to bacterial heat-shock protein 70 (Hsp70) elicit *in vivo* peptide-specific T-cell responses in the absence of adjuvant. Roman et al. teaches that hsp70 is an attractive candidate for specific vaccination against infectious diseases because hsp65 and hsp70 exert a strong helper activity *in vivo* when chemically conjugated to synthetic peptides. More specifically, Roman et al. discloses the construction of hsp70-pNP peptide complexes wherein the synthetic peptide is the influenza virus nucleoprotein (pNP) and the bacterial hsp70 is from *Mycobacterium tuberculosis* (see abstract). Roman et al. indicates that the influenza virus nucleoprotein was selected because it binds to *Mycobacterium tuberculosis* hsp70 and it is a good T-cell immunogen (page 487, 2nd col. 2nd ¶). Moreover, Roman et al. indicates that these complexes were highly effective for priming peptide-specific $CD4^+$ T-cell responses *in vivo* (page 487, 2nd col., 3rd ¶). Roman et al. does not teach fusion of the hsp to the influenza antigen.

Suzue (Journal of Immunology 1996 vol 156 pages 873-879) discloses a fusion protein comprising HIV p24 in fusion with hsp70. This composition elicited both humoral and cellular (cytolytic) responses when administered to mice in an adjuvant-free saline solution (see abstract,

Figure 1B). Saline is a pharmaceutically acceptable carrier or diluent. The fusion of the two proteins (hsp and p24) was determined to be necessary for proper immune stimulation (See paragraph bridging pages 876-877).

Taken together, the instant invention appears to be the same or slightly different from the prior art of combining stress proteins and an antigen of interest. Roman discloses the benefits of combining influenza antigens and a stress protein, hsp70, and Suzue discloses that those antigens in fusion with one another provide good T cell reactivity upon immunization. Suzue also indicates that a fusion between the moeities is necessary in order to induce the best immune response.

One of ordinary skill in the art at the time the invention was made would have been motivated to create a fusion protein comprising the influenza antigen in fusion with the stress protein so that the two moeities would be sure to stay together throughout the antigen presentation process, ensuring a better response. Suzue indicates this fusion strategy induces the strongest humoral and cellular immune responses. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

New Grounds of Rejection Necessitated by Amendment

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 54, 55, 58, and 61-67 are rejected under 35 U.S.C. 102(b) as being anticipated by Young (WO 94/29459 published 12/1994 PTO-1449 AL2).

Applicant has replaced the previously pending claims with claims limited to fusion proteins, but not limited in the nature of the stress protein. These amendments required a new search and the application of new art.

Young discloses fusion proteins of microbial stress proteins and an antigen of interest. In particular, Young sets forth that fusion proteins can be made between a stress protein and any antigen that one desires a specific immune response generated against. Antigens of viral pathogens, bacteria, or cancer cells are specifically contemplated at pages 3-4, and throughout the document. A variety of stress proteins are contemplated by Young, including mycobacterial stress proteins, and E. coli stress proteins (see Fig 1). Young discloses that stress proteins are among the major antigens available for presentation to T lymphocytes, and that antigens in fusion with stress proteins can invoke a specific T cell response to that antigen (pages 11-13). The fusion proteins are administered to mice in a pharmacologically acceptable carrier or diluent, phosphate buffered saline (Example 3 page 31).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102((e), f) or (g) prior art under 35 U.S.C. 103(a).

Claims 56-58 and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Young (WO 94/29459 published 12/1994 PTO-1449 AL2) as cited against claims 54, 55, 59 and 61-67 above, in view of Srivastava (US Patent 5,837,251, of record).

Claims 56-58 and 60 set forth that the particular antigens be from influenza, or from a variety of cancer associated antigens.

As set forth above, Young discloses fusion proteins of microbial stress proteins and an antigen of interest. In particular, Young sets forth that fusion proteins can be made between a stress protein and any antigen that one desires a specific immune response generated against. Antigens of viral pathogens, bacteria, or cancer cells are specifically contemplated at pages 3-4, and throughout the document. A variety of stress proteins are contemplated by Young, including

mycobacterial stress proteins, and E. coli stress proteins (see Fig 1). Young discloses that stress proteins are among the major antigens available for presentation to T lymphocytes, and that antigens in fusion with stress proteins can invoke a specific T cell response to that antigen (pages 11-13). The fusion proteins are administered to mice in a pharmacologically acceptable carrier or diluent, phosphate buffered saline (Example 3 page 31).

Srivastava discloses complexes of hsp proteins from the hsp60, hsp70 and hsp90 families in complex with antigens such as tumor antigens or influenza antigens. These complexes induce CD8+ (cytotoxic) CTL responses in vaccinated mice (columns 31 and 32). Claims 1 and 28 are representative claims. Srivastava specifically contemplates influenza antigens, for example, at column 24, section 5.4, and various cancer associated antigens such as tyrosinase, gp75, gp100 and mucins at column 13 lines 7-26.

Taken together, the instant invention appears to be the same or slightly different from the prior art of combining stress proteins and an antigen of interest. Srivastava discloses the benefits of combining viral antigens and cancer antigens with a stress protein, and Young discloses that those antigens in fusion with one another provide good T cell reactivity upon immunization.

One of ordinary skill in the art at the time the invention was made would have been motivated to create a fusion protein comprising the influenza or cancer antigen in fusion with the stress protein so that the two moeities would be sure to stay together throughout the antigen presentation process, ensuring a better response. Young indicates this fusion strategy induces the strongest humoral and cellular immune responses. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is prima facie obvious

to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mary K Zeman whose telephone number is (703) 305-7133. The examiner can be reached between the hours of 7:30 am and 5:00 pm Monday through Thursday, and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached at (703) 308 4028.

The fax number for this Art Unit is (703) 305-7401.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Tech Center receptionist whose telephone number is (703) 308-0196.

mkz
July 6, 2000

Marianne C. Allen
MARIANNE C. ALLEN
PRIMARY EXAMINER
GROUP 1600
AU1631